REMARKS

Claims 31, 80-82, 85, 91-104, 107, 110, 111, 115, and 121 are pending.

INFORMATION DISCLOSURE

Applicants are submitting herewith a Supplemental Information Disclosure Statement. Applicants wish particularly to draw the Examiner's attention to U.S. Patent No. 7,179,462 B2, as Ref. No. A15, for the Examiner's review and consideration.

THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, FOR LACK OF ENABLEMENT SHOULD BE WITHDRAWN

Claims 31, 80-82, 85, 91-104, 107, 110, 111, 115, and 121 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to allow one skilled in the relevant art to which it pertains to make and/or use the invention commensurate in scope with the claims.

Specifically, the Examiner maintained the rejections set forth in the previous Office Action (dated February 8, 2006), contending that the specification is not enabling for the claimed method of inhibiting an immune response with a compound that is either "an α2M receptor fragment" or "an α2M fragment," but acknowledging that the specification is enabling for a compound that is an antibody specific for the α2M receptor (see the Office Action at p. 2, para. 4). In addition, the Examiner raised two new grounds of rejection, contending that the specification is not enabling for (1) a method for treating an autoimmune disorder (which is encompassed by the claims) (see the Office Action at p. 9-11); or (2) any purified antibody, except a polyclonal anti-CD91 antibody (see the Office Action at p. 11-15).

In response, Applicants respectfully submit that the Examiner's arguments do not support a rejection of the pending claims under 35 U.S.C. § 112, first paragraph, for lack of enablement, for the reasons set forth below.

1. Enablement of "an α2M receptor fragment"

The Examiner contends that the specification is not enabling for anything more than an α2M receptor fragment which is "a polypeptide *consisting of the p80 fragment*" because "the exemplified binding experiments are not commensurate in scope" with anything more

than the p80 fragment (see the Office Action at p. 3 para. 2) (emphasis added). In response, Applicants respectfully maintain that the specification enables "an α2M receptor fragment" for the reasons set forth below.

In their Amendment filed May 8, 2006, Applicants maintained that the specification was enabling for the use of "an α2M receptor fragment" according to the claimed methods because (i) the structure of the α2M receptor is known in the art; (ii) the specification provides a specific example of a fragment having the desired activity, *i.e.*, the ability to interfere with the interaction of a heat shock protein with the α2M receptor, *i.e.*, the p80 fragment[1], which can be used as a positive control and/or as a starting point for identifying subfragments of p80 which retain the desired activity; (iii) the specification provides the amino acid sequence structure of other exemplary fragments of the α2M receptor that can be tested for the desired activity; and (iv) assays are described by the specification and known in the art which can be used to distinguish those fragments having the desired activity from those that do not (*e.g.*, receptor binding assays and antigen re-presentation assays).

The Examiner provides no explanation as to why the teachings in Applicants' specification combined with the knowledge in the art (*i.e.*, the known structure of the α2M receptor, the structure of exemplary α2M receptor fragments, including one, the p80 fragment, demonstrated by Applicants' specification to have the activity recited in the claims (*i.e.*, the ability to interfere with the interaction of a heat shock protein with the α2M receptor), and routine assays for determining whether a fragment interferes with the interaction of a heat shock protein with the α2M receptor) would not provide the skilled practitioner with the ability to make and use fragments of the α2M receptor, in addition to the

[1] As stated in Applicants' Amendment filed May 8, 2006, the specification demonstrates that an α2M receptor fragment, the p80 fragment, binds to heat shock proteins, is involved in the interaction between heat shock proteins and the α2M receptor which results in representation of heat shock protein-chaperoned antigenic peptide, and is involved in the α2M receptor immune activity (see the specification at p. 71, line 34 to p. 72, line 28 (describing cross-linking and affinity purification experiments showing that gp96 binds to the p80 fragment of the α2M receptor); p. 73, lines 13-19 (identifying the p80 fragment as an amino terminal fragment of the α2M receptor); and p. 72, line 29 to p. 73, line 28 (showing that antibodies raised against the p80 fragment of the α2M receptor inhibited representation of gp96-chaperoned antigenic peptides)). Thus, the results provided in the specification reasonably predict that the p80 fragment itself inhibits the interaction of heat shock protein with the α2M receptor, *e.g.*, by binding to available heat shock protein, thereby preventing the interaction between the heat shock protein and the α2M receptor. This is taught in the specification, *e.g.*, at p. 50, lines 10-13, which provides that an antagonist may be a peptide comprising at least 10 contiguous amino acids of the α2M receptor sequence which can bind to and "neutralize" an α2M receptor ligand such as a heat shock protein.

p80 fragment exemplified in the specification, according to the claimed methods and without undue experimentation. Applicants respectfully remind the Examiner that the specification *must* be taken as in compliance with the enablement requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. *In re Brana*, 51 F.3d 1560, 1566 (Fed. Cir. 1995) (emphasis in original). Thus, the burden is on the Examiner to provide evidence showing that one of ordinary skill in the art would have some basis to reasonably doubt Applicants' asserted utility on its face. *Id.* Applicants submit that there is nothing inherently unbelievable or scientifically implausible about their claim that, given the guidance in the specification and the p80 fragment as a starting point, fragments of the α2M receptor having the activity recited in the claims, in addition to the p80 fragment, can be identified by routine testing of the type that is typically done by protein chemists, *i.e.*, the ability to identify the minimal inhibitory fragment(s) of a polypeptide that has demonstrated the ability to interfere with the interaction between a receptor (such as the α2M receptor) and its ligand (such as a heat shock protein). To summarize, Applicants have demonstrated that the p80 fragment has the activity recited in the claims (*i.e.*, the ability to interfere with the interaction of a heat shock protein with the α2M receptor) and it is reasonable to expect that one or more subfragments of p80 will retain that activity. All that is required to identify such subfragments is routine experimentation, *i.e.*, testing subfragments of p80 to identify those having the desired activity using *e.g.*, binding assays and/or re-presentation assays which are both known in the art and taught by the specification. Since the Examiner has not provided any explanation regarding why one of skill in the art would reasonably doubt the ability to identify such fragments with routine experimentation, the Examiner has not met his burden with respect to establishing a *prima facie* case of lack of enablement on this basis.

The Examiner also relies on *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916 (Fed. Cir. 2004) to support his assertion that the screening assays taught by the specification do not enable the claimed invention because "they are merely a wish or plan for obtaining the claimed chemical invention" (see the Office Action at p. 3, para. 3). Applicants understand the Examiner to be referring to assays to test for the activity recited in the claims, *i.e.*, the ability to interfere with the interaction of a heat shock protein with the α2M receptor (*e.g.*, receptor binding assays and re-presentation assays). In response, Applicants first note that the court in *Rochester* did not reach the issue of enablement, having decided the case on a

finding of lack of written description. See *Rochester* at 930. Nevertheless, the Examiner's contention that the screening assays are "merely a wish or plan for obtaining the claimed chemical invention" cannot be reconciled with the specific teachings in the specification which provide the structure of the α2M receptor and a fragment of the receptor having the activity recited in the claims as well as the structure of additional, exemplary fragments. Thus, unlike the compound required to practice the claimed method in *Rochester*, which was defined only by its function, here the structure of the α2M receptor, as well as exemplary fragments of the receptor and how to make them, are described by Applicants' specification (see *e.g.*, the specification at p. 54, lines 1-27). In contrast, the specification in *Rochester* did not describe by structure, formula, chemical name, or physical properties a single example of a cyclooxygenase inhibitor for use in the claimed method. *Id.* at 927-28 (noting that "it is undisputed that the '850 patent does not disclose any compounds that can be used in the claimed methods"). Accordingly, Applicants submit that the Examiner's reliance on *Rochester* is misplaced and maintain that the present specification fully enables the claimed methods.

The Examiner further contends that "the specification does not provide the necessary guidance to the practitioner to enable the predictable making of the broadly claimed invention, *that is the ability to predictably distinguish between those fragments that will interfere with the interaction of a heat shock protein with the α2M receptor and those that will not*" (see the Office Action at p. 4 para. 1) (emphasis added). The Examiner provides no explanation as to why the routine assays described in the specification, such as receptor binding assays and re-presentation assays, would not provide the skilled practitioner with the ability to distinguish interfering fragments from non-interfering fragments, especially in view of the correlation between *in vitro* and *in vivo* activity discussed below. Applicants submit that there is nothing inherently unbelievable or scientifically implausible about the claim that the skilled practitioner can distinguish interfering from non-interfering fragments using the assays described in the specification or other routine assays known in the art. Applicants refer the Examiner to the discussion of the rule set forth in *In re Brana* above and submit that the Examiner has failed to meet his burden with respect to establishing a *prima facie* case of lack of enablement on this basis.

The evidence provided by Applicants shows that compounds that interfere with heat shock protein-α2M receptor interactions *in vitro* have *in vitro* activity that correlates with *in vivo* activity

The Examiner further contends that Applicants have failed to establish that there was, at the time of filing, a reasonable correlation between the ability of a compound to inhibit a cytotoxic T cell response in an *in vitro* representation assay and its ability to inhibit an *in vivo* immune response (see the Office Action at p. 4 para. 2). In response, Applicants maintain that a reasonable correlation between the ability of a compound to elicit or inhibit a T cell response as measured by an *in vitro* re-presentation assay and the compound's activity *in vivo*, *i.e.*, its ability to elicit or inhibit an immune response *in vivo*, as measured by a recognized assay or model system, was established in the art at the time of filing for the reasons described below.

Applicants have provided ample evidence that a compound's activity in an *in vitro* re-presentation assay had been demonstrated to correlate with its *in vivo* activity, this demonstration being in 1995, well before the filing date of the instant application in 2000 (see the Amendment dated June 9, 2005 ("the 2005 Amendment") at p. 12, last para. to p. 13, first para., and Suto and Srivastava, 1995, *Science* 269:1585-88 ("Suto 1995" Ref. No. "CL" of Applicants' Information Disclosure Statement)). Applicants also direct the Examiner's attention to a declaration of Dr. Hans-Georg Rammensee, Ph.D ("Declaration") submitted herewith, in support of this position. In the Declaration, Dr. Rammensee, citing Suto 1995, states that it was known in the art at June 2000 that mammalian heat shock proteins can elicit an antigen-specific immune response against peptide complexed to the heat shock protein and that this immune response is characterized by a peptide-specific activation of T cells, which was measured either in *vitro* as a specific T cell response against the peptide (*i.e.*, re-presentation assay), or *in vivo* as protective immunity against transplanted tumor cells in the mouse tumor transplantation model (see Declaration at ¶ 8). Applicants submit that these established *in vitro* and *in vivo* assays to measure specific T cell response can also be applied to assay the ability of compounds that interfere with the interaction of the α2M receptor and a heat shock protein to inhibit an antigen-specific immune response elicited by the heat shock protein, as demonstrated in the present specification and by various publications (see Declaration at ¶¶ 10-14). Moreover, the publications discussed below further validate that a compound's activity in an *in vitro* re-presentation assay correlates with its *in vivo* activity.

Applicants have submitted evidence from several post-filing references to substantiate their claim of a correlation between the activity of a compound in an *in vitro* re-presentation assay and its ability to inhibit or elicit an immune response *in vivo*. The use of such post-filing date evidence is proper. See *In re Brana* 51 F.3d 1560, 1567 n.19 (Fed. Cir. 1995) (stating that a post-filing date declaration setting forth test results substantiating utility "pertains to the accuracy of a statement already in the specification. It does not render an insufficient disclosure enabling, but instead goes to prove that the disclosure was in fact enabling when filed (*i.e.*, demonstrated utility)." (internal citations omitted)).

The references relied upon by Applicants were:

1. Basu *et al.*, 2001 *Immunity*, "CD91 is a common receptor for heat shock proteins gp96, hsp90, hsp70, and calreticulin," 14:303-313 ("Basu 2001"), Information Disclosure Statement ("IDS") Ref. No. C04;
2. Binder *et al.*, 2002 "Naturally formed or artificially reconstituted non-covalent alpha-2-macroglobulin-peptide complexes elicit CD91-dependent cellular immunity," *Cancer Immunity* 2:16-23 ("Binder 2002"), IDS Ref. No. C03; and
3. Binder and Srivastava, 2004 "Essential Role of CD91 in re-presentation of gp96-chaperoned peptides," *Proc. Natl. Acad. Sci. U.S.A.* 6128-6133 ("Binder 2004"), IDS Ref. No. C02.

Applicants further submit herewith Chandawarkar *et al.*, 2004 "Immune modulation with high-dose heat shock protein gp96: therapy of murine autoimmune diabetes and encephalomyelitis," *Int'l Immunol.* 16:315-324 ("Chandawarkar 2004"), enclosed as Ref. No. C117 in Applicants' Supplemental Information Disclosure Statement, as an additional reference relied on by Applicants. Applicants maintain that these references demonstrate a correlation between the ability of a compound to inhibit an immune response in an *in vitro* re-presentation assay (*i.e.*, an antigen-specific T cell response) and the ability of the compound to inhibit an *in vivo* immune response, for the reasons stated below. In addition, the Examiner's attention is directed to the Declaration submitted herewith (declaration of Dr. Hans-Georg Rammensee, Ph.D), in support of Applicants' position.

In their November 8, 2004 Amendment ("the 2004 Amendment"), Applicants submitted Binder 2004 which demonstrates a correlation between the activity of a compound, α2M, in an *in vitro* re-presentation assay and its activity *in vivo* (see Binder 2004 Fig. 3B at p. 6131; the 2004 Amendment at p. 12, paras. 2-3; and Declaration at ¶ 13). Specifically, Binder 2004 shows that the activation of antigen-specific T cells by gp96 complexed peptide

is inhibited by α2M and also by another ligand of the α2M receptor, RAP, in an *in vitro* re-presentation assay (see Binder 2004 Fig. 2A at p. 6130). Dr. Rammensee states that this *in vitro* activity was also demonstrated to correlate with the ability to inhibit antigen-specific T cell activation *in vivo* (see Declaration at ¶ 13). Mice were immunized with gp96-peptide complexes alone, or in the presence of either α2M or an anti-α2M receptor antibody and antigen presenting cells were then isolated from the draining lymph nodes of the immunized mice. The results demonstrated that the antigen presenting cells from mice immunized in the presence of either α2M or the antibody were unable to activate T cells (see Binder 2004 at p. 6130, col. 2 to p. 6131, col. 1, and Fig. 3). Thus, Dr. Rammensee concludes that Binder 2004 shows a correlation between the inhibitory activity of a compound, α2M, in an *in vitro* re-presentation assay and its ability to inhibit an *in vivo* immune response (see Declaration at ¶ 13).

As explained by Dr. Rammensee indicates, Binder 2004 also demonstrates such a correlation for another substance, polyclonal anti-α2M receptor antibody (also referred to in the literature as "anti-CD91" antibody) (see Declaration at ¶ 12; and the 2004 Amendment at p. 12, last para. to p. 13, para. 1). Specifically, Binder 2004 shows that a polyclonal anti-α2M receptor antibody, a compound shown by Applicants' specification to inhibit an immune response elicited by gp96 in an *in vitro* re-presentation assay, also inhibits the immune response elicited by gp96 in two different assays of *in vivo* activity (see Declaration at ¶ 12). The first assay was described above. To summarize, mice were immunized with gp96-peptide complexes either alone or in combination with an anti-α2M receptor antibody (or α2M, as discussed above) (see Binder 2004 Fig. 3B at p. 6131). Cells from the lymph nodes of immunized mice were used for stimulation of antigen-specific T cells. The results in Fig. 3B demonstrate that both the antibody and α2M effectively inhibited the activation of antigen-specific T cells by the gp96-peptide complexes. The second assay was a tumor rejection assay (see Binder 2004 Fig. 5 at p. 6133). In this assay, mice were immunized with gp96-peptide complexes obtained from tumor cells, either alone or in combination with anti-α2M receptor antibody and then injected with tumor cells. (see Binder 2004 at p. 6131, col. 2, para. 3, and Fig. 5 at p. 6133). Mice immunized with gp96 complexes from the cancer cells showed very little tumor growth (see Fig. 5, middle row, left panel). However, this anti-tumor immunity was effectively inhibited by co-administration with the anti-α2M receptor antibody (but not by co-administration of the control antibody) (see Fig. 5, middle row,

second and third panels from left). These data, combined with the teachings of Applicants' specification, demonstrate a correlation between the inhibitory activity of anti-α2M receptor antibodies in an *in vitro* re-presentation assay, *i.e.*, their ability to inhibit an antigen-specific T cell response *in vitro*, and their ability to inhibit an immune response *in vivo*, *i.e.*, to inhibit an antigen-specific T cell activation or to inhibit tumor growth *in vivo* (see Declaration at ¶ 12).

These results were also substantiated by Binder 2002 which demonstrates that a polyclonal anti-α2M receptor antibody inhibits the protective immunity elicited by gp96 *in vivo*, *i.e.*, in a mouse tumor transplantation model system (see Binder 2002 at p. 19 and Fig. 3; and Declaration at ¶ 12). In the Declaration, Dr. Rammensee discusses the *in vivo* experiment presented in Binder 2002 where mice were immunized with gp96-peptide complexes plus either the anti-α2M receptor antibody or an isotype control antibody (see Declaration at ¶ 12). Additional antibody was administered at the same site each day for two days after each immunization. Live tumor cells were injected intradermally one week after the last immunization and tumor growth (volume) was measured over a period of about 20 days. As shown in Figure 3, top left panel of Binder 2002, mice immunized with gp96-peptide complexes and the isotype control antibody experienced very little tumor growth. In contrast, mice immunized with gp96-peptide complexes and the anti-α2M receptor antibody showed considerable tumor growth, demonstrating that the antibody blocked the protective immunity of the gp96-peptide complexes (see Figure 3, bottom left panel; and Declaration at ¶ 12).

Further substantiation of the results in Applicants' specification is provided by Basu 2001, which demonstrates that a number of compounds that interfere with the interaction of a heat shock protein with the α2M receptor also inhibit an immune response (*i.e.*, a T cell response) as measured by an *in vitro* re-presentation assay. In Basu 2001, antigen presenting cells were pulsed with gp96 complexed with antigenic peptide (AH1/19) in the presence of increasing concentrations of either gp96, hsp90, hsp70, or serum albumin, and T cell activation was measured by cytokine release (see Basu 2001 at p. 305, col. 2, para. 2-3, and Fig. 5A). The results demonstrated a dose-dependent inhibition of T cell activation with increasing concentrations of each of the inhibitors, gp96, hsp90, or hsp70. Basu 2001 further demonstrated that α2M and a monoclonal anti-α2M receptor antibody (two compounds that interfere with the interaction between heat shock protein and the α2M receptor) both

effectively blocked re-presentation of the antigenic peptide by each of the heat shock proteins, gp96, hsp90, hsp70, and calreticulin (see Basu 2001 at p. 305, col. 2, para 4, to p. 306, col. 2, para. 1, and Fig. 5B and 5C; and p.312, col. 1 para. 1 (anti-CD91 antibody was clone 5A6 from Progen)). Thus, Dr. Rammensee concludes that Basu 2001 provides a further demonstration that compounds that interfere with the interaction between a heat shock protein and the α2M receptor effectively inhibit an immune response and that gp96, hsp90, hsp70, α2M, and an antibody against the α2M receptor are all effective in this context (see Declaration at ¶ 14).

As explained by Dr. Rammensee, Chandawarkar 2004 provides evidence validating the correlation between the *in vitro* activity of gp96 to inhibit T cell activation in a re-presentation assay and the *in vivo* activity of gp96 to block anti-tumor activity *in vivo* (see Declaration at ¶ 14). In particular, Chandawarkar 2004 demonstrates that high-dose gp96 effectively blocked anti-tumor immunity generated by gp96 (in the form of gp96-peptide complexes[2] derived from Meth A fibrosarcoma) in mice (see Chandawarkar 2004 at p. 616, col. 2 to p. 618, col. 1 and Figs. 1 and 2). In Chandawarkar 2004, a high-dose (90 μg) of gp96 derived from Meth A fibrosarcoma or normal liver administered concurrently with an optimal immunizing low-dose (10 μg) of gp96 derived from Meth A fibrosarcoma effectively suppressed tumor immunity of mice challenged with live Meth A cells (see Chandawarkar 2004 at p. 616, col. 1 to p. 617, col. 1 and Fig. 1). Further, this immunosuppressive high-dose of gp96 was only effective when it was administered concurrently with or subsequent to the optimal immunizing low-dose of gp96 derived from Meth A fibrosarcoma (see Chandawarkar 2004 at p. 617, col. 1 to p. 618, col. 1 and Fig. 2). Thus, Dr. Rammensee concludes that the *in vivo* data in Chandawarkar 2004 combined with the *in vitro* data in Basu 2001, showing that gp96 inhibited an antigen-specific T cell response in an *in vitro* re-

[2] Although Chandawarkar 2004 does not expressly refer to "complexes" of gp96 and peptide, it would be clear one of skill in the art that complexes are in fact being used because Chandawarkar 2004 references Srivastava *et al.* (*Proc. Natl. Acad. Sci. U.S.A.* 1986 "Tumor rejection antigens of chemically induced sarcomas of inbred mice," 83:3407-3411, see *e.g.* p. 3408, col. 1 para. 2 to col. 2 para. 4, "Srivastava," enclosed as Ref. No. C120), for the purification of gp96 (see Chandawarkar 2004 at p. 616, col. 1, para. 2). Srivastava teaches the purification of gp96 from the cytosol or soluble membrane fraction of Meth A cells using a combination of affinity and ion-exchange chromatography (*i.e.*, Concavalin A, DEAE-Sepharose, and Mono Q FPLC). By way of clarification, Applicant notes that gp96 is referred to as "Meth A TRA" in Srivastava because it was initially isolated based on its activity as a "Tumor Rejection Antigen." It was known in the art at the time of filing the instant application that the purification method used in Srivastava produces gp96-peptide complexes (see *e.g.*, U.S. Patent No. 5,837,251, issued 11/17/98, at col. 15, line 29 to col. 16, line 47, Ref. No. AB). Thus, the skilled worker would rightly conclude that the gp96 preparations used in Chandawarkar 2004 are in fact complexes of gp96 and peptide.

presentation assay, demonstrate a correlation between the inhibitory activity of gp96 *in vitro* and its ability to inhibit an immune response *in vivo* (see Declaration at ¶ 14).

In summary, Dr. Rammensee concludes that the data for gp96, α2M, and anti-α2M receptor antibodies, as described in the Declaration, demonstrate a correlation between the *in vitro* activity and the *in vivo* activity of compounds that are expected to interfere with the heat shock protein-α2M receptor interaction (see Declaration at ¶ 15). The post-filing evidence of Basu 2001, Binder 2002, Binder 2004, and Chandawarkar 2004 demonstrates a correlation between the *in vitro* activity and the *in vivo* activity of three substances that are expected to interfere with a heat shock protein-α2M receptor interaction, gp96, α2M, and anti-α2M receptor antibodies, using established assays (*i.e.*, *in vitro* re-presentation assay and *in vivo* mouse tumor transplantation model system) that were taught in the art well before June 2000, as evidenced by Suto 1995 (see Declaration at ¶¶ 8 and 15).

The Examiner does not dispute that Applicants have demonstrated such a correlation for an anti-α2M receptor antibody (see the Office Action at p. 4 para. 2). Nevertheless, the Examiner contends that Applicants' argument was not persuasive because the references relied upon did not teach which, if any, α2M receptor fragments or α2M fragments interfere with heat shock protein-α2M receptor interaction *in vitro* or *in vivo* (see the Office Action at p. 4 para. 2, and at p. 7, para. 2). Applicants understand the Examiner to be requiring that they demonstrate a correlation between *in vitro* and *in vivo* activity for each of the compounds recited in the claims, *i.e.*, for an α2M receptor fragment and an α2M fragment, as well as for an α2M receptor antibody.

In response, Applicants submit that such a requirement is improper because 35 U.S.C. § 112 does not require *in vivo* testing of every species within a claim, provided there is a reasonable correlation between *in vitro* results and *in vivo* activity. *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1565 (Fed. Cir. 1996). Applicants have shown that a reasonable correlation exists by demonstrating a correlation for the genus of compounds that interfere with the interaction of a heat shock protein with an α2M receptor. Applicants have demonstrated this by coming forward with both *in vitro* and *in vivo* evidence for three examples of such interfering compounds, gp96, α2M, and anti-α2M receptor antibodies.

In view of the data put forward by Applicants for the genus of compounds that interferes with the interaction of a heat shock protein with an α2M receptor, Applicants maintain that it is reasonable to expect that the compounds recited in the claims, *i.e.*, antibodies and α2M receptor fragments and α2M fragments, would demonstrate a similar correlation between their activity in an *in vitro* re-presentation assay and their *in vivo* activity because, like the antibodies, the fragments having *in vitro* activity will be those that interfere with the interaction between a heat shock protein and the α2M receptor. It is reasonable to expect that a fragment having such interfering activity *in vitro* will have similar activity *in vivo*, and thus will inhibit an immune response elicited by the interaction of heat shock protein with the α2M receptor, as was demonstrated for the anti-α2M receptor antibodies, for α2M, and for gp96.

The Examiner does not dispute that Applicants have demonstrated a reasonable correlation between a compound's activity in a re-presentation assay and its ability to inhibit or elicit an immune response *in vivo*. Accordingly, Applicants submit that the Examiner's continued rejection of the claims on this basis can not be supported and respectfully request that this rejection be withdrawn.

2. Alleged unpredictability with respect to claimed use of "an α2M fragment"

The Examiner contends that "given the unpredictability in the art, in the absence of objective evidence no one of skill would believe it more likely than not that the invention would function as claimed" with respect to α2M fragments (see the Office Action at p. 5, para. 3). Specifically, the Examiner dismisses Applicants' claim that, in view of the ability of α2M to interfere with the interaction of a heat shock protein with the α2M receptor and inhibit an immune response (*i.e.*, as demonstrated by Applicants' specification at p. 73, lines 20-28, and by the post-filing evidence of Basu 2001 (Fig. 5B) and Binder 2004 (Fig. 1, Fig. 2A, and Fig. 3B)), it is reasonable to expect that one or more fragments of α2M will also exhibit this activity, and further that it is a matter of routine skill to identify such fragments given the known structure of α2M and the availability of routine screening assays to test for such activity.

The Examiner provides no basis, other than a conclusory statement that the art is unpredictable, for his reasoning that one of skill would doubt that the invention would

function as claimed with respect to an α2M fragment that interferes with the interaction of a heat shock protein with the α2M receptor. Applicants have provided evidence that α2M is able to interfere directly with the interaction between a heat shock protein and the α2M receptor, *i.e.*, as measured by a competitive binding assay (see Binder 2004, Fig. 1A) and that α2M inhibits an immune response elicited by heat shock protein (see Applicants' specification at p. 73, lines 20-28; Binder 2004 Figs. 2A and 3B; and Basu 2001 Fig. 5B). Given this data provided by Applicants demonstrating that α2M itself has the activity recited in the claims, Applicants maintain that there is nothing inherently unbelievable or scientifically implausible about their position that it is a matter of routine skill to identify one or more fragments of α2M that retain the activity which Applicants have demonstrated for α2M itself. Moreover, Applicants maintain that the specification provides sufficient guidance for the genus of α2M fragments with the desired activity by describing twelve representative species and by describing a combination of identifying characteristics of the genus including amino acid sequence structure and functional characteristics that correlate with the sequence structure. For example, the specification provides twelve exemplary α2M fragments, SEQ ID NOS: 8-19, at page 51, lines 16-22. The specification also provides the specific portions of α2M that interact with the α2M receptor, namely amino acids 1314-1451, described at page 13, lines 27-29, Fig. 7B, and in the references provided at page 3, line 34 through page 4, line 7, including Salvesent *et al.*, 1992 *FEBS Lett.* 313:198-202 and Holtet *et al.*, 1994 *FEBS Lett.* 344:242-246. Finally, the specification teaches that there is an art-recognized correlation between the structure of the α2M receptor-binding domain identified in Figure 7B as amino acids 1314-1451, and the functional ability of α2M to bind to the α2M receptor. Moreover, at page 4, lines 8-13, the specification provides that an "[a]lignment of α2M receptor ligands identifies a conserved domain" which "spans amino acids 1366-1392 of human α2M" and that two of those conserved residues are required for binding to the α2M receptor, as demonstrated by Nielsen *et al.*, 1996 *J. Biol. Chem.* 271:12909-12912.

Applicants submit that the kind of experimentation required to test whether a particular α2M fragment interferes with the interaction between a heat shock protein and the α2M receptor is of the type routinely conducted by protein chemists to identify the minimal inhibitory fragment(s) of a polypeptide that has been demonstrated to interfere with the interaction between a receptor and its ligand. In the absence of any evidence other than the

Examiner's opinion to the contrary, Applicants submit that the Examiner's continued rejection of the claims on this basis can not be supported (see *In re Brana*, discussed above), and Applicants respectfully request that this rejection be withdrawn.

The Examiner also contends that "the specification does not provide the necessary guidance to the practitioner to enable the predictable making of the broadly claimed invention, *that is the ability to predictably distinguish between those fragments that will interfere with the interaction of a heat shock protein with the α2M receptor from those that will not*" (OA p. 6 para. 1) (emphasis added). The Examiner provides no explanation regarding why the routine assays described in the specification (*e.g.*, receptor binding assays and re-presentation assays; see the specification at Section 5.2.1, p. 27-32 (receptor-ligand binding assays) and the re-presentation assays described in the specific example at p. 69, lines 27-33) combined with the knowledge in the art would not provide the skilled practitioner with the ability to distinguish interfering fragments from non-interfering fragments. Accordingly, as discussed above, the Examiner has failed to establish a *prima facie* case of lack of enablement on this basis and Applicants respectfully request that this rejection be withdrawn.

The Examiner also contends that the evidence of a correlation between the *in vitro* re-presentation assays and an *in vivo* immune response provided by Applicants is not persuasive "because Binder et al. (2002, 2004, IDS) teach one example where administration of anti-CD91 antibody inhibited an immune response in a mouse model, but did not exemplify inhibition of immune response with any α2M fragments or α2M receptor fragments" (OA at p. 7, para 2). As with the rejection pertaining to α2M receptor fragments discussed above, Applicants understand the Examiner to be improperly requiring *in vivo* data in support of each compound recited in the claims. Applicants maintain that they have demonstrated a reasonable correlation between a compound's activity in an *in vitro* re-presentation assay and its ability to elicit or inhibit an immune response *in vivo* for the reasons discussed above, and 35 U.S.C. § 112 requires no more. Applicants point out that, as discussed above, they have demonstrated a correlation between the activity of a compound in an *in vitro* re-presentation assay and its ability to inhibit or elicit an immune response *in vivo*, not only for anti-α2M receptor antibodies but also for α2M and heat shock proteins.

3. <u>Alleged unpredictability due to lack of correlation with a clinical response</u>

The Examiner does not dispute that Applicants have demonstrated a reasonable correlation between the ability of a compound to modulate an immune response in an *in vitro* re-presentation assay and its ability to similarly modulate an immune response *in vivo*. However, the Examiner contends that this evidence is not persuasive because there is "a poor correlation between induction of specific T-cells and the clinical responses" (see the Office Action at p. 7 para. 2, citing Bellone *et al.*, 1999 "Cancer immunotherapy: synthetic and natural peptides in the balance," *Immunology Today* 20:457-462 ("Bellone")).

Applicants understand this rejection to be based on an alleged lack of utility for the claimed method under 35 U.S.C. § 101 and § 112 (see *Rasmusson v. Smithkline Beecham Corp.*, WL 1501450 at page 3 (Fed. Cir. 2005) ("the how to use prong of section 112 incorporates as a matter of law the requirement of 35 U.S.C. § 101 that the specification disclose as a matter of fact a practical utility for the invention."). Bellone teaches that, although synthetic and natural peptides used as cancer vaccines are often able to elicit an antigen-specific T cell response *in vivo*, this T cell response does not generally correlate with a *clinical response* to the tumor in cancer immunotherapy (see Bellone at p. 457, col. 1, last para. and p. 459, col. 1, first para.). First, Applicants point out that the claims are not directed to a "clinical response" to a tumor, but rather to inhibiting an immune response. Thus, whatever Bellone may suggest about the correlation between the ability of a compound to elicit an *in vivo* T cell response and its ability to elicit a clinical response to a tumor, Bellone does not call into question the correlation between a compound's activity in an *in vitro* re-presentation assay and its ability to elicit an *in vivo* immune response, which is the relevant correlation with respect to the claimed methods.

To the extent that the Examiner's rejection suggests that Applicants must present data of clinical efficacy in humans for the claimed methods of inhibiting an immune response, Applicants further note that it is improper to request such evidence of safety and efficacy in the treatment of humans, when the evidence that has been presented reasonably correlates with the asserted utility, as it does in the instant case. See *e.g.*, *In re Brana*, 51 F.3d 1560, 1567 (Fed. Cir. 1995)("Testing for the full safety and effectiveness of a prosthetic device is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings.")(quoting *Scott v. Finney*, 34 F.3d 1058, 1063 (Fed. Cir. 1994)). Instead, the court stated that

> Usefulness in patent law, and in particular in the context of pharmaceutical inventions, *necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans.*

Id. at 1568 (internal citations omitted)(emphasis added). The court further stated that "proof of an alleged pharmaceutical property for a compound by statistically significant tests with standard experimental animals is sufficient to establish utility." *Id.* at 1567 (quoting *In re Krimmel*, 292 F.2d 948 (CCPA 1962) for the proposition that "one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment in humans.").

In summary, Applicants maintain that they have put forth sufficient evidence demonstrating that the ability of a compound to modulate an immune response in an *in vitro* representation assay is reasonably correlated with its ability to similarly modulate an immune response *in vivo*, and 35 U.S.C. § 112 requires no more.

4. <u>Alleged unpredictability for methods of inhibiting an immune response in an autoimmune disorder</u>

The Examiner contends that "neither the specification nor the art of record has established a nexus between administering any of the claimed molecules to inhibiting an immune response in an autoimmune disorder" (see the Office Action at p. 9, paras. 3-4) and that "in the absence of objective evidence that the claimed invention will function in the *in vivo* environment in a human to in fact effectively treat an autoimmune disease" there is no reasonable prediction that the methods will function as claimed in a human.

In response, Applicants submit that the data demonstrating the ability to block an immune response are reasonably predictive of efficacy in treating an autoimmune disease or disorder. In support of this position, Applicants direct the Examiner's attention to the Declaration submit herewith (a declaration of Dr. Hans-Georg Rammensee, Ph.D) which demonstrates that there is a well-grounded scientific basis for the use of the compounds recited in the claims for inhibiting an immune response for the treatment of an autoimmune disease or disorder. Specifically, the Declaration explains the following:

(1) the immune response generated by heat shock proteins ("hsp") is mediated by antigen-specific T cell activation, which is a fundamental mechanism for immunity generally,

and which is directly involved in the pathogenesis of autoimmune diseases, such that compounds that inhibit T cell activation are reasonably predicted to be useful for the treatment of an autoimmune disease or disorder;

(2) each of the compounds recited in the claims interferes with (*i.e.*, is an antagonist of) the interaction between hsp and an α2M receptor, and each has either been shown to inhibit the immune response generated by heat shock proteins (*i.e.*, α2M receptor fragment and anti-α2M receptor antibodies), or is reasonably predicted to do so based on its ability to interfere with the interaction between hsp and an α2M receptor (*i.e.*, α2M fragment); and

(3) an antagonist of hsp-α2M receptor binding, gp96, has been demonstrated to delay the onset of autoimmune disease in two well-known animal models, the experimental autoimmune encephalomyelitis ("EAE") model, and the non-obese diabetic ("NOD") mouse model.

(A) Heat shock proteins can elicit antigen-specific T cell activity against complexed peptide and antigen-specific T cell activity is directly involved in the pathogenesis of autoimmune diseases

As demonstrated by Suto 1995, discussed above and in the Declaration, it was known in the art at the earliest claimed priority date of this application (June 2, 2000) that mammalian heat shock proteins (also referred to in the literature as "stress proteins") can elicit an antigen-specific immune response against peptide complexed to the heat shock protein (see Declaration at ¶ 8 and Suto 1995 at p. 1585, col. 1). This immune response is characterized by a peptide-specific activation of T cells, which was measured either *in vitro* as a specific T cell response against the peptide (*i.e.*, in a re-presentation assay), or *in vivo* as protective immunity against transplanted tumor cells in the mouse tumor transplantation model. The importance of T cell activation in generating anti-tumor immunity in this model system was already well-established at the time of filing (see *e.g.*, Abbas, Lichtman, and Pober, 1991 *Cellular and Molecular Immunology*, W.B. Saunders Co., Philadelphia (Chapters 15-18) ("Abbas") at p. 347, col. 1 para. 3; see also p. 338-340, enclosed as Ref. No. C115 of Applicants' Supplemental Information Disclosure Statement, discussing the T cell response generated against tumor-specific transplantation antigens in this model system).

In the Declaration, Dr. Rammensee explains how T cell activation is an important mechanism for immunity generally (see Declaration at ¶ 9). For example, $CD8^+$ T cells are the principal mechanism of specific immunity against established viral infections (see Abbas at p. 310, col. 1, para. 2-3) and the rejection of transplanted allografts is mediated by $CD8^+$ and $CD4^+$ T cells (see Abbas at p. 320, col. 1 to col. 2). With respect to autoimmune diseases and disorders, T cell responses are directly involved in causing tissue damage in a number of organ-specific autoimmune diseases (see *e.g.*, Janeway, Travers, Walport, and Shlomchick, 2001 Immunobiology, 5th ed., Garland Publishing, New York (p. 6-7) ("Janeway") at p. 7, para. 2, enclosed as Ref. No. C116 of Applicants' Supplemental Information Disclosure Statement).

Dr. Rammensee further explains that the direct involvement of T cells in the pathogenesis of autoimmune diseases has also been demonstrated in two well-known animal models of autoimmunity, the EAE model, which is a mouse model for human multiple sclerosis and human encephalomyelitis, and the NOD model, which is a mouse model for insulin-dependent diabetes mellitus (see Declaration at ¶ 9). Pathogenesis in these models is caused by autoreactive $CD4^+$ and $CD8^+$ T cells against specific antigens. In the NOD model, pathogenesis is caused by autoreactive $CD4^+$ and $CD8^+$ T cells against antigens of pancreatic islet cells (see *e.g.*, Chandawarkar 2004 at p. 619, col. 1, lines 1-2 and Abbas at p. 367, Box 18-3), and in the EAE model, pathogenesis is caused by autoreactive $CD4^+$ and $CD8^+$ T cells against myelin basic protein (see *e.g.*, Steinman, L., 2001 *J. Exp. Med.*, "Myelin-specific $CD8^+$ T cells in the pathogenesis of experimental allergic encephalitis and multiple sclerosis," 194:F27-F30 ("Steinman 2001") at p. F27, col. 1, para. 1, and col. 2, para. 2, enclosed as Ref. No. C118 of Applicants' Supplemental Information Disclosure Statement). The immune response generated by mammalian heat shock proteins also comprises antigen-specific $CD8^+$ and $CD4^+$ T cells (see *e.g.*, SenGupta *et al.*, 2004 *J. Immunol.*, "Heat shock protein-mediated cross-presentation of exogenous HIV antigen on HLA Class I and Class II," 173:1987-1993 ("SenGupta 2004") at p. 1987, col. 2 first para., enclosed as Ref. No. C119 of Applicants' Supplemental Information Disclosure Statement, and references 17-19 cited therein). Accordingly, the immune response generated by mammalian heat shock proteins, as an antigen-specific T cell response, is an important mechanism both of immunity generally, and presumably of pathogenesis in autoimmune diseases and disorders (see Declaration at ¶ 9). Since T cell activation is directly involved in the pathogenesis of autoimmune diseases,

compounds that inhibit T cell activation in the context of an autoimmune disease or disorder would reasonably be expected to have efficacy in treating the autoimmune disease or disorder (see Declaration at ¶ 9).

(B) The present application discloses that the α2M receptor is a receptor for heat shock proteins and that antagonists of hsp-α2M receptor binding inhibit T cell activation by heat shock proteins

The present application teaches that heat shock proteins bind to a specific receptor on antigen presenting cells, the α2M receptor, also referred to in the art as "CD91" (see *e.g.*, the Example at pages 69-75 of the specification), and that receptor binding is required for the immune response generated by heat shock proteins. Specifically, data in the specification demonstrate that antagonists of hsp-α2M receptor binding effectively block antigen-specific T cell activation by heat shock proteins (see Declaration at ¶ 10). This is demonstrated for compounds which interfere with the interaction of the α2M receptor with a heat shock protein, including antibodies (*i.e.*, anti-α2M receptor antibodies) and a competitive inhibitor of heat shock protein binding to the α2M receptor (*i.e.*, α2M[3]). Specifically, the specification demonstrates that antiserum against the 80 kilodalton hsp-binding fragment of the α2M receptor inhibited T cell activation by gp96 (see the specification at p. 72, line 29 to p. 73 line 12 and Fig. 2; and Declaration at ¶ 10). The specification also demonstrates that increasing concentrations of α2M, a recognized ligand of the α2M receptor, effectively inhibited T cell activation by heat shock proteins (see the specification at p. 73, lines 20-28, and Fig. 4). As noted by Dr. Rammensee, these results show that compounds which interfere with the interaction of the α2M receptor and a heat shock protein are able to block the immune response, *i.e.*, the antigen-specific T cell activation, generated by heat shock proteins, which is an important mechanism of immunity (see Declaration at ¶ 10).

Dr. Rammensee notes in the Declaration, by way of clarification, that the assay used in the specification to measure an immune response is an assay for T cell activation, referred to as a "re-presentation" assay (see Declaration at ¶ 11). The name "re-presentation" reflects the knowledge in the art at the earliest claimed priority date for the application that the peptide complexed to heat shock protein does not directly stimulate T cell activation but

[3] See Binder 2004 at p. 6129, Fig. 1, demonstrating that α2M, and another known ligand of the α2M receptor, RAP, competitively inhibit heat shock protein binding to the CD91 receptor.

instead must first be taken up and re-presented to the T cells by antigen presenting cells in complex with MHC molecules (*see* Suto 1995 cited and explained by Binder 2004 at p. 6130, col. 1, para. 2 and col. 2, para. 2; and Declaration at ¶ 11). This was first demonstrated by data showing that antigen complexed with heat shock protein was channeled into the endogenous antigen-processing pathway of antigen presenting cells, re-presented by Class I MHC molecules, and recognized by cytotoxic T cells (*see* Suto 1995 *supra*). It has also been demonstrated that antigen complexed with heat shock protein is re-presented by Class II MHC molecules (*see* SenGupta at p. 1987, col. 1, para. 1, and references cited therein). However, the quantitative measure of this assay is one of T cell activation, which is a measure of an immune response, not of peptide bound to MHC molecules (see Declaration at ¶ 11).

The data in Applicant's specification demonstrating that compounds that interfere with the interaction of a heat shock protein with the α2M receptor inhibit the immune response generated by the heat shock protein are confirmed and extended by the post-filing evidence provided in Binder 2002, Binder 2004, Basu 2001, and Chandawarkar 2004, each of which was discussed above and in the Declaration. To summarize, Binder 2002 demonstrates that a polyclonal anti-CD91 antibody effectively blocked the anti-tumor immunity generated by heat shock proteins in the mouse tumor transplantation model system (see Binder 2002 at p. 19 and Fig. 3; and Declaration at ¶ 12). As discussed above, anti-tumor immunity in the tumor transplantation model system is known to involve T cell activation. Binder 2004 confirms these results in another tumor transplantation model system using a polyclonal anti-CD91 antibody and gp96-peptide complexes purified from the cancer cells (see Binder 2004 at p. 6131, col. 2, para. 3, and Fig. 5 at p. 6133; and Declaration at ¶ 12). Binder 2004 also demonstrates that other compounds that interfere with the interaction of a heat shock protein with the α2M receptor, *i.e.*, the α2M receptor ligands RAP and α2M, effectively block the immune response generated by heat shock proteins (*i.e.*, activation of antigen-specific T cells) (see Declaration at ¶ 13). Basu 2001 also demonstrates that a number of compounds that interfere with the interaction of a heat shock protein with the α2M receptor, *i.e.*, the heat shock proteins gp96, hsp90, and hsp70, as ligands of the α2M receptor, and the known α2M receptor ligands, RAP and α2M, as well as a monoclonal anti-α2M receptor antibody, each effectively block the immune response generated by heat shock proteins (see Declaration at ¶

14). Chandawarkar 2004 demonstrates that high-dose gp96 effectively blocked anti-tumor immunity generated by gp96 in mice.

In summary, the data in Applicant's specification, combined with the post-filing evidence of Binder 2002, Binder 2004, Basu 2001, and Chandawarkar 2004, provide a reasonable expectation of success for the use of the compounds recited in the claims for inhibiting an immune response, specifically an antigen-specific T cell response, which is an important mechanism in the pathogenesis of autoimmune diseases and disorders, as discussed by Dr. Rammensee in the Declaration (see Declaration at ¶ 15).

(C) Treatment of autoimmune diseases: An antagonist of hsp-α2M receptor binding delays the onset of autoimmune disease in two animal models.

Applicants submit that the disclosure in the specification and the published data discussed in section 2 above, which demonstrate that the compounds recited in the claims, as antagonists of hsp-α2M receptor binding, are effective in blocking an immune response, *i.e.*, an antigen-specific T cell response, are reasonably convincing of the asserted use to treat an autoimmune disease or disorder, as discussed by Dr. Rammensee in the Declaration (see Declaration at ¶ 15). In further support of this position, Applicant directs the Examiner to the Declaration and the post-filing evidence provided in Chandawarkar 2004 (Ref. No. C117 of Applicants' Supplemental Information Disclosure Statement), discussed above and in the Declaration. Chandawarkar 2004 demonstrates that a compound that interferes with the interaction of a heat shock protein with the α2M receptor, *i.e.*, gp96, effectively inhibits the onset of autoimmune disease in two well-known animals models, the experimental autoimmune encephalomyelitis ("EAE") model, and the non-obese diabetic ("NOD") mouse model (see Declaration at ¶ 16). The fact that gp96 interferes with the interaction of a heat shock protein with the α2M receptor is demonstrated by Basu 2001, discussed above. In the EAE model, the autoimmune disease is induced by either myelin basic protein ("MBP") or proteolipid protein ("PLP") (see Chandawarkar 2004 at p. 618, col. 2, para. 2-3). Mice were first immunized with MBP and treated with gp96 (in the form of gp96-peptide complexes[4])

[4] As discussed previously, although Chandawarkar 2004 does not expressly refer to "complexes" of gp96 and peptide, it would be clear one of skill in the art that complexes are in fact being used because Chandawarkar 2004 references Srivastava *et al.* (*Proc. Natl. Acad. Sci. U.S.A.* 1986 "Tumor rejection antigens of chemically induced sarcomas of inbred mice," 83:3407-3411, see *e.g.* p. 3408, col. 1 para. 2 to col. 2 para. 4, "Srivastava,"

obtained from normal mouse liver. Control animals were either left untreated or treated with phosphorylase b (an unrelated protein), saline, or lipopolysaccharide. The results demonstrated that 60-75% of the control animals developed progressive paralysis of all four limbs by day 60-post immunization with MBP. In contrast, only 20-40% of the mice treated with gp96 developed paralysis (see Chandawarkar 2004 at p. 618, col. 2, para. 2 and Fig. 3A). Similar results were obtained when EAE was induced using PLP (see Chandawarkar 2004 at p. 618, col. 2, para. 3 and Fig. 3B). In the NOD mouse model, mice were immunized twice, one week apart, with gp96 obtained from liver or pancreas of NOD mice (see Chandawarkar 2004 at p. 619, col. 1, para. 2). Control animals were treated with phosphate-buffered saline or left untreated. All of the control animals began to develop diabetes between 10 and 14 weeks of age and all were diabetic by 20 weeks of age, as measured by monitoring urine sugar levels (see Chandawarkar 2004 at p. 619, col. 1, para. 2-3, and Fig. 4 at p. 620). In contrast, 80% of the mice immunized with 100 ug of gp96 from either liver or pancreas remained disease-free for the entire period of the study, or 24 weeks of age. As noted by Chandawarkar, "[t]he results described in this study show that high-dose gp96 elicits antigen-specific suppression in a wide array of models of immunity, including autoimmunity" (see Chandawarkar 2004 at p. 623, col. 1, para. 3). As stated by Dr. Rammensee, these results confirm the data in Applicants' specification demonstrating a sound scientific basis for the use of the compounds recited in the claims for treating an autoimmune disease or disorder, because the compounds recited in the claims are, like high-dose gp96, compounds which have either been demonstrated to interfere with the interaction of a heat shock protein with the α2M receptor or which are reasonably expected to do so (see Declaration at ¶¶ 16 and 17).

The Examiner contends that, since T cells are already activated in autoimmune disease, one of skill in the art would not predict that interference with the interaction of a heat shock protein with the α2M receptor would be effective in treating autoimmune disease because Binder 2004 suggests that inhibition of the interaction between a heat shock protein with the α2M receptor "must take place prior to active representation of the peptides on

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enclosed as Ref. No. C120), for the purification of gp96 (see Chandawarkar 2004 at p. 616, col. 1, para. 2). It was known in the art at the time of filing the instant application that the purification method used in Srivastava produces gp96-peptide complexes (see *e.g.*, U.S. Patent No. 5,837,251, issued 11/17/98, at col. 15, line 29 to col. 16, line 47, Ref. No. AB). Thus, the skilled worker would rightly conclude that the gp96 preparations used in Chandawarkar 2004 are in fact complexes of gp96 and peptide.

antigen presenting cells" (citing to Binder 2004, Fig. 5) (see the Office Action at p. 10, para. 2).

In response, Applicants refer the Examiner to Chandawarkar 2004, discussed above, which demonstrates that, contrary to the Examiner's assumption, inhibition of an immune response by compounds that interfere with the interaction of a heat shock protein and the α2M receptor occurs in the presence of an ongoing immune response (see Chandawarkar 2004 at p. 617, col. 1, para. 2 to p. 618, col. 1 para. 1). Specifically, Chandawarkar 2004 shows that mice receiving the inhibitor (high dose gp96, "HDgp96") at the same time as the immunizing dose of gp96-peptide complexes exhibited maximal suppression of the immune response against the tumor cells in a tumor transplantation model system like the one used in Binder 2004 (see Chandawarkar 2004 at p. 618, col. 1, para. 1 and Fig. 2B, Group 3). In contrast, mice receiving the inhibitor *before* the immunizing dose of gp96-peptide complexes showed no suppression (see Chandawarkar 2004 at Fig. 2B, Group 5). The authors conclude from their data that the immunosuppressive activity of the inhibitor "requires prior existence of an immune response" (Chandawarkar 2004 at p. 617, col. 1 to p. 618, col. 1). Thus, the data in Binder 2004 cited by the Examiner, which shows that an inhibitor (in this case an anti-α2M receptor antibody) given at the same time as the immunizing dose of gp96-peptide complexes suppresses the immune response elicited by the complexes, are consistent with the results of Chandawarkar 2004 and with the conclusion drawn by the authors of that paper, namely that suppression is observed in the context of a preexisting immune response.

In addition, the authors of Chandawarkar 2004 further state that the results presented in Figure 2 are consistent with observations in the NOD mouse model:

> [T]reatment of 4- to 5-week-old NOD mice with high-dose gp96 was ineffective at suppressing onset of diabetes, even as 8- to 10-week-old mice treated in the same manner were protected (data not shown). Based on the timing of onset of insulitis (that precedes destruction of β cells), it has been surmised that the autoimmune process in NOD mice does not begin until 6 weeks of age. Treatment with suppressive doses of gp96 before that times does not suppress diabetogenesis.

(Chandawarkar 2004 at p. 621, col. 1)(internal citation omitted). Further, Applicants also refer the Examiner to U.S. Patent No. 6,007,821 (the '821 patent), IDS Ref. No. A01, which substantiates the NOD mouse model data discussed in Chandawarkar 2004. In the '821 patent, NOD mice were treated with 25 μg (Figs. 3B and 3C) or 100 μg (Figs. 3A and 3D) of

gp96 derived from pancreas and liver at 5 weeks (Figs. 3A and 3B) or 8 weeks (Figs. 3C and 3D) of age (see the '821 patent at Figs. 3A-D; and col. 5, lines 22-37). The results presented in Figures 3A-3D of the '821 patent indicate that commencement of the therapy with gp96-peptide complexes was most effective in providing protection from diabetes at around 8 weeks of age (see the '821 patent at col. 26, lines 43-49; Figs. 3A-D; and col. 5, lines 22-37). Further, the '821 patent discloses that "gp96 mediated suppression [of diabetes] depends on the combined prior appearance of autoantigen(s) and activated T cells reactive against the autoantigen(s)." (the '821 patent at col. 26, lines 49-52). Thus, contrary to the Examiner's contention, Chandawarkar 2004 and the '821 patent demonstrate that the immunosuppressive activity of the inhibitor is observed in the context of a preexisting immune response.

5. Alleged unpredictability for use of a monoclonal antibody in the claimed methods

The Examiner contends that, while the specification is enabling for the use of a *polyclonal* antibody specific for the α2M receptor in the claimed methods, it does not provide enablement for any purified antibody, including monoclonal antibodies, specific for α2M receptor (see the Office Action at p. 11 para. 3 to p. 12 para. 1). Specifically, the Examiner contends that "[o]ne cannot extrapolate the teachings of the specification to the scope of the claims because one cannot predict that any antibody, including monoclonal antibodies, specific for the α2M receptor can interfere with the interaction of a heat shock protein with α2M receptor in an amount effective to inhibit an immune response in a human *because of the unpredictability of a given antibody to function in a manner similarly to another given antibody although the antibodies are directed to the same target.*" (see the Office Action at p. 13 para. 4) (emphasis added).

In support of this position, the Examiner refers to a teaching in Harlow and Lane (1988) *Antibodies A Laboratory Manual*, Ch. 6 p. 139-243, at p. 142, first para. and Table 6.1 ("Harlow and Lane"). In the paragraph cited to by the Examiner, Harlow and Lane teach that monoclonal antibodies are "often more time-consuming and costly to prepare than polyclonal antibodies" and that "producing exactly the right set of monoclonal antibodies is often a difficult and laborious job." Applicants note that the date of this reference is 12 years prior to the earliest claimed priority date of the instant application, June 2, 2000, and as such it does not accurately represent the state of the art at the time of filing.

Applicants note that the test for the amount of experimentation which may be considered "undue" under section 112, first paragraph, "is not merely quantitative, since a considerable amount of experimentation is permissible, *if it is merely routine*, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988) (internal quotations omitted) (emphasis added). Applicants submit that, contrary to the Examiner's position, the skill in the art of monoclonal antibody technology at the relevant time, *i.e.*, circa June 2, 2000, was such that the experimentation required to make a monoclonal anti-α2M receptor antibody having the activity recited in the claims was routine, as evidenced by the commercial availability of such antibodies.

Publications demonstrate that monoclonal antibodies that can be used in the claimed methods are obtainable

The Examiner contends that "[n]either the specification nor the art of record teach that a monoclonal antibody to the α2M receptor can be used in the claimed method to inhibit an immune response in a human by interfering with the interaction of a heat shock protein with the α2M receptor" and further that undue experimentation is required "to identify the domain of the α2M receptor to be targeted by the monoclonal antibody and then to isolate the monoclonal antibody" for use in the claimed methods (see the Office Action at p. 14).

Applicants have demonstrated that polyclonal anti-α2M receptor antibodies can interfere with the interaction of a heat shock protein and the α2M receptor. This indicates that the epitope of the α2M receptor which is recognized by such interfering antibodies is available to the immune system. Accordingly, one of skill in the art would reasonably expect to be able to raise monoclonal antibodies against the same epitope.

Moreover, examples of such monoclonal antibodies have been obtained. Applicants note that publications of record teach a monoclonal antibody that can be used in the claimed methods. Specifically, Binder *et al.*, August 2000, *Nature Immunol.* 1:151-155 ("Binder 2000"), IDS Ref. No. C89, also teaches a monoclonal antibody which can be used in the claimed methods (see Binder 2000 at p. 153, col. 2, para. 3 (teaching that a monoclonal antibody against the α2M receptor inhibits re-presentation of peptides complexed to gp96), and at p. 155, col. 1, para. 6 (teaching that the monoclonal antibody was purchased from BioMac GmbH, Germany and thus showing that a suitable anti-CD91 monoclonal antibody

was commercially available)). Basu 2001, discussed above, teaches a monoclonal antibody specific for the α2M receptor that inhibits the immune response elicited by the heat shock proteins gp96, hsp90, hsp70, and calreticulin in a re-presentation assay (see Basu 2001 Figure 5C and p. 306, col. 1 para. 2; see Basu 2001 at p. 312, col. 1, para. 1 (teaching that the anti-CD91 monoclonal antibody was purchased from PROGEN, Heidelberg, Germany and thus showing that a suitable anti-CD91 monoclonal antibody was commercially available)). Thus, these publications disclose monoclonal anti-α2M receptor antibodies which inhibit an immune response elicited by heat shock proteins in an *in vitro* re-presentation assay. These publications show that anti-α2M receptor monoclonal antibodies which inhibit re-presentation *in vitro* can be obtained, supporting the enablement of the full scope of the claimed use of anti-α2M receptor antibodies for inhibiting an immune response in a human, given the demonstrated correlation between activity in an *in vitro* re-presentation assay and the ability to elicit *in vivo* immune response, as discussed above. Applicants respectfully remind the Examiner that it is not necessary to show efficacy in humans to satisfy the enablement and utility requirements of 35 U.S.C. section 112. In addition, there is no reason to believe that obtaining such monoclonal antibodies would entail undue experimentation (especially since such antibodies were commercially available).

Moreover, based on the data in Applicants' specification and the evidence discussed above, Applicants submit that it is reasonably predictable that any antibody that interferes with the interaction of a heat shock protein with the α2M receptor will also inhibit an immune response elicited by the heat shock protein, because these data demonstrate that a number of different compounds which interfere with the interaction of a heat shock protein with the α2M receptor, including both monoclonal and polyclonal antibodies, do in fact inhibit an immune response elicited by the heat shock protein.

<u>It is not necessary to know the domain or epitope targeted by anti-α2M receptor antibodies in order to make and use the same</u>

In response to the Examiner's contention that undue experimentation is required "to identify the domain of the α2M receptor to be targeted by the monoclonal antibody and then to isolate the monoclonal antibody" for use in the claimed methods, Applicants submit that it is not necessary to know the identity of the domain (or epitope) of the α2M receptor to which heat shock proteins bind in order to make a monoclonal antibody which can interfere with the

interaction between a heat shock protein and the α2M receptor. All that is required is routine screening of anti-α2M receptor antibodies to identify those having the desired activity, *e.g.*, using binding assays or re-presentation assays as described in the specification (see *e.g.*, the specification at Section 5.2.1, p. 27-32 (receptor-ligand binding assays) and the re-presentation assays described in the specific example at p. 69, lines 27-33).

Applicants submit that, given the high degree of skill in the art of monoclonal antibody technology and the commercial availability of anti-α2M receptor antibodies, one of skill in the art would be able to obtain, without undue experimentation, monoclonal anti-α2M receptor antibodies that interfere with the interaction of a heat shock protein with the α2M receptor, and use such antibodies to inhibit the immune response elicited by the heat shock protein-α2M receptor interaction.

In view of the foregoing remarks, Applicants respectfully request the Examiner's withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, for lack of enablement.

THE REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, FOR LACK OF WRITTEN DESCRIPTION SHOULD BE WITHDRAWN

Claims 31, 80-82, 85, 91-93, 102, 107, 110, and 121 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking an adequate written description in the specification.

1. Description of anti-α2M receptor antibody

The Examiner contends that the specification does not describe an antibody for use according to the claimed methods that satisfies either the *Lilly* or *Enzo* standards (citing to *Univ. of California v. Eli Lilly and Co.*, 119 F.3d 1559 (Fed. Cir. 1997) and *Enzo Biochem Inc. v. GenProbe Inc.*, 296 F.3d 1316 (Fed. Cir. 2002) (see the Office Action at p. 17, last para. to p. 19, first para.). Specifically, the Examiner contends that, per *Enzo*, either a complete or partial structure is required, or identified physical or chemical characteristics coupled with a known correlation between structure and function (see the Office Action at p. 18 para. 1); or that, per *Lilly*, a representative number of species, or structural features common to members of the genus, is required (see the Office Action at p. 18 para. 2).

In response, Applicants submit that the teachings in the specification satisfy the written description requirement with respect to an anti-α2M receptor antibody for use in the claimed methods. In particular, Applicants' specification teaches that the antigen for the

antibody is the α2M receptor, which is fully characterized in the prior art both by its sequence structure and physical properties (see *e.g.*, the specification at p. 3, line 18 to p.4 line 26). Applicants' specification also fully describes a fragment of the α2M receptor, the p80 fragment, by its amino acid sequence structure and physical properties, which fragment can be used as an antigen to produce anti-α2M receptor antibodies for use in the claimed methods (see the specification at p. 13, line 34 to p. 14, line 5, description of Figure 8A, and at p.73, lines 13-19). In fact, the specification teaches a specific example of a polyclonal antibody which can be used in the claimed methods and which was produced using the p80 fragment as immunogen (see the specification at p. 72, line 29 to p. 73, line 12). Applicants submit that the disclosure of a fully characterized antigen is all that is required to satisfy the written description requirement with respect to the antibodies for use in the claimed methods. This is because nothing more is required to claim the *antibody itself*, much less the use of the antibody in a claimed method. See *Noelle v. Lederman*, 69 U.S.P.Q.2d 1508, 1514, n.1 (Fed. Cir. 2004) ("based on our past precedent, as long as an applicant has disclosed a "*fully characterized* antigen," either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository, the applicant can then claim an antibody by its binding affinity to that described antigen.") (quoting *Enzo Biochem* at 970) (emphasis in original). Moreover, the specification, Basu 2001, and Binder 2000, discussed above, show that the instant disclosure of the antigen is sufficient description of antibodies to said antigen that interfere with the interaction of a heat shock protein with the α2M receptor.

In summary, Applicants submit that the specification satisfies the written description requirement for anti-α2M receptor antibodies for use in the claimed methods in view of the fact that both the α2M receptor and a fragment of the α2M receptor that can be used as an immunogen for making the antibodies are fully characterized either in the prior art or in Applicants' specification.

2. Description of α2M fragments

The Examiner stated that, upon review and reconsideration, the rejection of claims 31, 80-82, 85, 91, 94, 95, 103, 107, 110, and 111 under 35 U.S.C. 112, first paragraph, as allegedly lacking adequate written description is reimposed (see the Office Action at p. 19, para. 3). Specifically, the Examiner contends that the specification does not provide an

adequate written description of an α2M fragment that interferes with and inhibits an immune response *in vivo* in humans (see the Office Action at p. 22, para. 1).

Applicants maintain that the specification provides sufficient description of the genus of α2M fragments by describing twelve representative species and by describing a combination of identifying characteristics of the genus including amino acid sequence structure and functional characteristics that correlate with the sequence structure. For example, the specification provides twelve exemplary α2M fragments, SEQ ID NOS: 8-19, at page 51, lines 16-22. The specification also provides the specific portions of α2M that interact with the α2M receptor, namely amino acids 1314-1451, described at page 13, lines 27-29, Fig. 7B, and in the references provided at page 3, line 34 through page 4, line 7, including Salvesent *et al.*, 1992, *FEBS Lett.* 313:198-202 and Holtet *et al.*, 1994, *FEBS Lett.* 344:242-246. Finally, the specification teaches that there is an art-recognized correlation between the structure of the α2M receptor-binding domain identified in Figure 7B as amino acids 1314-1451, and the functional ability of α2M to bind to the α2M receptor. Specifically, at page 4, lines 8-13, the specification provides that an "[a]lignment of α2M receptor ligands identifies a conserved domain" which "spans amino acids 1366-1392 of human α2M" and that two of those conserved residues are required for binding to the α2M receptor, as demonstrated by Nielsen *et al.*, 1996, *J. Biol. Chem.* 271:12909-912. Accordingly, appropriate written description is provided for the α2M fragments of claims 31 and 71.

Thus, the specification provides twelve specific examples of the genus of α2M fragments encompassed by the claims. The specification further provides distinguishing attributes of the genus, *e.g.*, the specific portion of the α2M protein from which the fragments are derived and an art-recognized correlation between the structure of that portion of the α2M protein and the function of binding to the α2M receptor.

Nevertheless, the Examiner contends that "Applicant's [sic] reliance on general structure (*i.e.*, α2M receptor binding domain) is inadequate because specific not general disclosure is required . . ." Applicants do not understand the Examiner's characterization of the α2M receptor binding domain of α2M as a "general" disclosure, since, as discussed above, the specific portions of α2M that interact with the α2M receptor, namely amino acids 1314-1451 and the conserved region therein of amino acids 1366-1392, are described in the specification at page 13, lines 27-29, in Fig. 7B, and in the references provided at page 3, line

34 through page 4, line 7, including Salvesent *et al.*, 1992, *FEBS Lett.* 313:198-202 and Holtet *et al.*, 1994, *FEBS Lett.* 344:242-246. Accordingly, Applicants maintain that the written description requirement of 35 U.S.C. § 112, first paragraph, is satisfied with respect to the genus of α2M fragments recited in the claims.

2. Description of α2M receptor fragments

The Examiner stated that, upon review and reconsideration, the rejection of claims 31, 80-82, 85, 91, 96-99, 104, 107, 110, and 115 under 35 U.S.C. 112, first paragraph, as allegedly lacking adequate written description is reimposed (see the Office Action at p. 19, para. 2, p. 24, para. 3, and p. 29, para. 1). Specifically, the Examiner contends that the specification does not describe an α2M receptor fragment for use in the claimed methods in a manner that satisfies either the *Lilly* or *Enzo* standard.

First, the Examiner contends that the specification does not provide any complete or partial structure of an α2M receptor fragment that interferes with the interaction of a heat shock protein and an α2M receptor. The Examiner acknowledges that the specification discloses the p80 fragment, which is a fragment of the α2M receptor that interferes with the interaction of a heat shock protein with the α2M receptor in an *in vitro* re-presentation assay (as demonstrated by Applicants' specification, *e.g.*, at page 71, lines 34-37 to page 73, line 28). The Examiner nevertheless contends that "this does not provide a description of α2M receptor fragments that interferes [sic] with the interaction of heat shock protein with the α2M receptor and inhibits an immune response *in vivo* in a human that would satisfy the standard set out in *Enzo*." However, the p80 fragment taught by the specification is the complete structure of an α2M receptor fragment that interferes with the interaction of heat shock protein with the α2M receptor and is reasonably expected to inhibit an immune response *in vitro* (*i.e.*, an antigen specific T cell response as measured in a re-presentation assay), and Applicants have demonstrated a reasonable correlation between the ability of a compound to inhibit an immune response in an *in vitro* re-presentation assay and its ability to inhibit an immune response *in vivo*. In view of this, Applicants fail to understand the grounds for the Examiner's contention that the description of the p80 fragment is insufficient.

Second, the Examiner contends that the specification does not describe a "representative number" of α2M receptor fragments or "structural features common to the members of the genus" sufficient to satisfy the *Lilly* standard (see the Office Action at p. 27,

para. 2 to p. 28). Applicants addressed this rejection in the Amendment filed June 9, 2005 ("the 2005 Amendment"). In the 2005 Amendment, Applicants pointed out that the specification provides *eight* exemplary α2M receptor fragments, namely, three corresponding to SEQ ID NOS: 20-22 (see page 54, lines 15-27, of the specification), four corresponding to SEQ ID NOS: 54-57 (see page 73, lines 13-19, page 13, lines 5-9, and Fig. 3C of the specification), and the p80 α2M receptor fragment. SEQ ID NOS: 20-22 are within the CI cluster of the α2M receptor, and are fragments of p80. SEQ ID NOS: 54-57 are located between the CI and CII clusters, and are fragments of p80. The p80 fragment corresponds to an N-terminal fragment of the α2M receptor which includes the CI cluster and additional sequence between the CI and CII clusters (see page 73, lines 13-19, and Figure 8B of the specification). The specification also teaches that the p80 fragment binds to the heat shock protein gp96 (see page 71, line 34 to page 73, lines 1-12, and page 75, lines 1-28, of the specification).

Applicants maintain that in view of the evidence of binding between the heat shock protein gp96 and the p80 fragment, a reasonable expectation exists that α2M receptor fragments comprising sequence derived from the p80 fragment will interfere with the interaction of an HSP with the receptor, as specified by the claims. Such fragments are exemplified by p80 itself and the seven additional sequences recited above.

In the 2005 Amendment, Applicants also pointed out that the specification provides distinguishing attributes of the fragments which comprise HSP-binding portions of the α2M receptor, *e.g.*, at page 54, lines 7-15, and in Figure 8B. For example, the specification provides that the HSP-binding portion of the α2M receptor consists of, or comprises, at least one complement repeat or a cluster of complement repeats, preferably CI-II. The specification also provides structural details as to the length of the HSP-binding fragment of the α2M receptor, *e.g.*, that it can consist of at least 10, 20, 30, 40, or most preferably 80 amino acids; or that such fragments are not larger than 40-45 or 80-90 amino acids. Finally, the specification describes a particular embodiment of an α2M receptor fragment, namely an 80 kDa fragment, which binds to the heat shock protein gp96 and is reasonably expected to inhibit the re-presentation of gp96 by antigen presenting cells (see *e.g.*, the specification at page 71, lines 34-37 to page 73, line 28, and the portion of the α2M receptor sequence highlighted in bold in Fig. 8B, corresponding to amino acid residues 327-346, described at page 14, lines 2-3).

To summarize, the specification satisfies the Lilly standard by provides *eight* exemplary α2M receptor fragments as well as a correlation between the α2M receptor fragments and HSP-binding, provided by the specific example of the p80 fragment. The specification further provides distinguishing attributes of the genus, *e.g.*, the specific portion of the α2M receptor protein from which the fragments are derived, their preferred length, and an art-recognized correlation between the structure of that portion of the α2M receptor protein and the ligand-binding function of the α2M receptor.

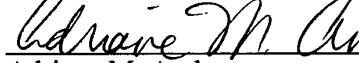
CONCLUSION

Applicants believe that the present claims meet all of the requirements for patentability. Consideration of the foregoing remarks is respectfully requested.

If a telephone interview would be of assistance in advancing prosecution of the subject application, Applicants' undersigned attorney invites the Examiner to telephone her at the number provided below.

Respectfully submitted,

Date: March 21, 2007



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